REMARKS

Claims 1-8 are pending in the above-identified application and stand ready for further action on the merits.

Interview with Examiner

Applicants appreciate the Examiner's courtesy in holding a personal interview on June 29, 2005 with Applicants' representative, John W. Bailey. The Examiner's statement in the Interview Summary correctly sets forth the subject matter discussed in the interview.

Claim Rejections Under 35 USC § 103

Claims 1-8 have been rejected under 35 USC § 103(a) as being unpatentable over Fujioka et al. US '547 (US 5,851,547) in combination with Hudson et al. EP '410 (EP 0009410 A2). Reconsideration and withdraw of this rejection is respectfully requested based on the following considerations.

Legal Standard for Determining Prima Facie Obviousness

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

"There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art." *In re Rouffet,* 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998) (The combination of the references taught every element of the claimed invention, however without a motivation to combine, a rejection based on a *prima facie* case of obvious was held improper.). The level of skill in the art cannot be relied upon to provide the suggestion to combine references. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999).

"In determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the reference before him to make the proposed substitution, combination, or other modification." *In re Linter*, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972).

Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. "The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." *In re Kotzab,* 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000). See also *In re Lee,* 277 F.3d 1338, 1342-44, 61

USPQ2d 1430, 1433-34 (Fed. Cir. 2002); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

The Present Invention and Its Advantages

The present invention provides for controlled release preparations having multi-layer structures. The preparations more particularly relate to controlled drug-release formulations having multi-layer structures, wherein one or more drugs can separately be released with a different behavior *in vivo*, for the purpose of effectively exhibiting the efficacy thereof.

In the present specification, experiments are carried out and reported between preparations of the present invention and comparative preparations. As seen upon reviewing experiments 1-4 at pages 20-21 of the specification, and Figures 2-5 referred to therein, the Examiner can easily see that the compositions of the present invention possess advantageous properties, and allow one to easily release one or more drugs separately with different behaviors in vivo.

Distinctions over the Cited Art

The following distinctions over the cited art of Fujioka et al. US '547 in combination with Hudson et al. EP '410 are divided into two sections, which are titled "(I). Newly Presented Comments" and "(II). Previously Presented Comments".

The following section titled "Previously Presented Comments" contains comments taken from the Applicants prior reply of February 4, 2004. This has been done since the outstanding Office Action sets forth basically an identical rejection to that previously responded to in the February 4, 2004 reply. As such, these comments from the earlier reply are also pertinent to the current rejection.

(I). Newly Presented Comments

The formulation of Fujioka et al. contains a "water-soluble drug" in an inner layer (claim 1, paragraph (a)). The release mechanism of a water soluble drug dispersed in a hydrophobic polymer is based on "**channeling and cracking phenomenon**" (column 1, lines 47-56, and column 8, lines 61-64). In the Fujioka et al formulation, only an end(s) of the inner layer comes into contact with the external environment, and as a result only a limited region is initially subject to channeling (Column 9, lines 1-6). In addition, the outer layer, due to its characteristic functional design, is able to exercise suitable control of inner layer cracking (column 9, lines 6-8). The outer layer can control water infiltration of inner layer (column 5, lines 10-11) through control swelling thereof (column 5, lines 16-19). Also, the outer layer is essential to prevent a very rapid initial release of the drug (column 10, lines 9-12). Through these means, the formulation of Fujioka et al. is able to exercise suitable control of water infiltration into the inner layer and is thereby able to achieve long-term zero-order release (column 9, lines 8-11).

On the other hand, the formulation of Hudson et al. contains estradiol in a coating of the inert core (claim 1, paragraph (b), page 4, lines 1-2 and 18-19). Constant release of estradiol is achieved by **diffusion** thereof through the coating to the surface (page 4, lines 2-4 and 22-24). The inert core does not participate in the control of drug release, but only serves as a base to provide a size and shape of the implant placed under the skin of the ruminant animal (page 3, lines 19-20). According to Martindale 29th Ed. (page 1407, right column, 9083-y, "Oestradiol"), estradiol is "practically insoluble in water". Further, Ferguson et al. (*Journal of Controlled Release*, 8 (1988), 45-54) discusses a commercial product of the Hudson formulation and describes that estradiol is dispersed

as discrete crystals or solid particles in the matrix (page 45, right column, the section of "Theory", and Figure 1 on page 46). Ferguson et al. also indicate that estradiol is released by diffusion, not by dissolution, and that the diffusional process occurs through the matrix itself, not through pores or channels within the matrix (page 45, right column, the bottom line and page 46, left column). In view of the teachings of Martindale 29th Ed. and Ferguson et al., noted above, it is clear that constant release of the drug in the Hudson et al. formulation results from the property of estradiol being practically insoluble in water and that it diffuses through the polydimethylsiloxane silicone rubber, and not from the core-coating structure of the formulation.

Thus the formulation of Fujioka et al. and Hudson et al. are completely different in their technical solutions to achieve constant release of their drug. Therefore, those skilled in the art would not be motivated to apply the technical solution of Hudson et al. to the formulation of Fujioka et al., although the Examiner in contradiction asserts that the it is neither novel nor nonobvious to place a drug in the outer layer of a coated drug formulation (page 2, lines 16-18 of the office action).

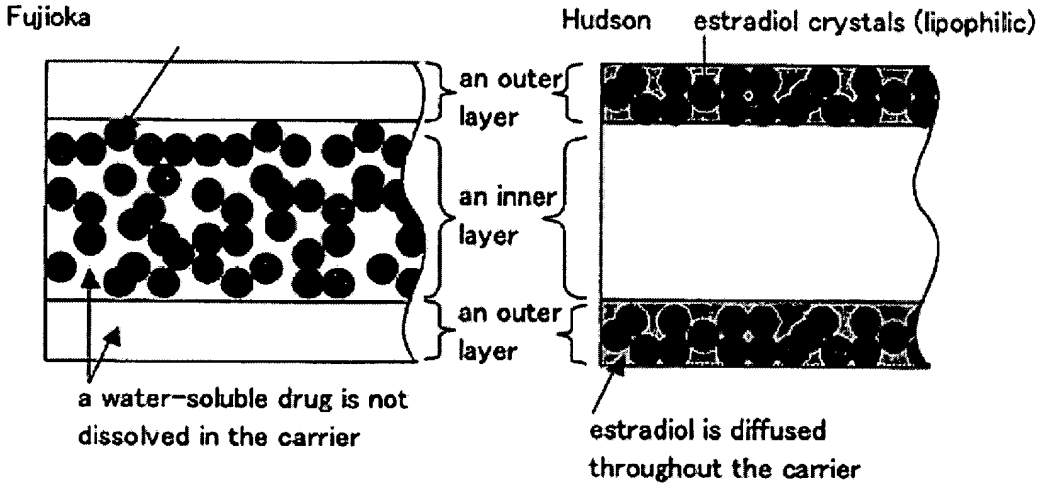
The Examiner also refers to the description of column 10, lines 9-12 of Fujioka et al. and states that it would be reasonable to provide a formulation wherein a drug is placed in the outer layer as taught by Hudson et al. when there is a desire to provide a very rapid release (page 2, lines 18-20 of the Office Action). However, Fujioka et al. relate to "a drug delivery formulation which releases a water-soluble drug intracorporeally over a prolonged period of time at a nearly constant rate" (column 3, lines 61-64), and teach the solution to prevent a very rapid release (column 10, lines 9-12). Thus, Fujioka et al. teach away providing such a very rapid initial release, and the Examiner's contrary perspective of the description in column 10, lines 9-12 cannot be derived or obtained without knowledge of the present invention.

The Examiner further recites specific drugs such as insulin, antibiotics and anti-inflammatory agents as requiring an immediate initial dose followed by a sustained release (page 2, bottom line and page 3, line 2 of the Office Action). However, Fujioka et al. only provide the technical solution to release of a drug at a nearly constant rate (column 3, lines 61-64). Thus, Fujioka et al. teach away from the release of drugs at an immediate initial dose, which serves to show that the outstanding rejection is based in part on an impermissible level of hindsight reconstruction on the Examiner's part.

Accordingly, the present invention cannot be derived from the teachings of the cited art, without knowledge of the present invention as claimed.

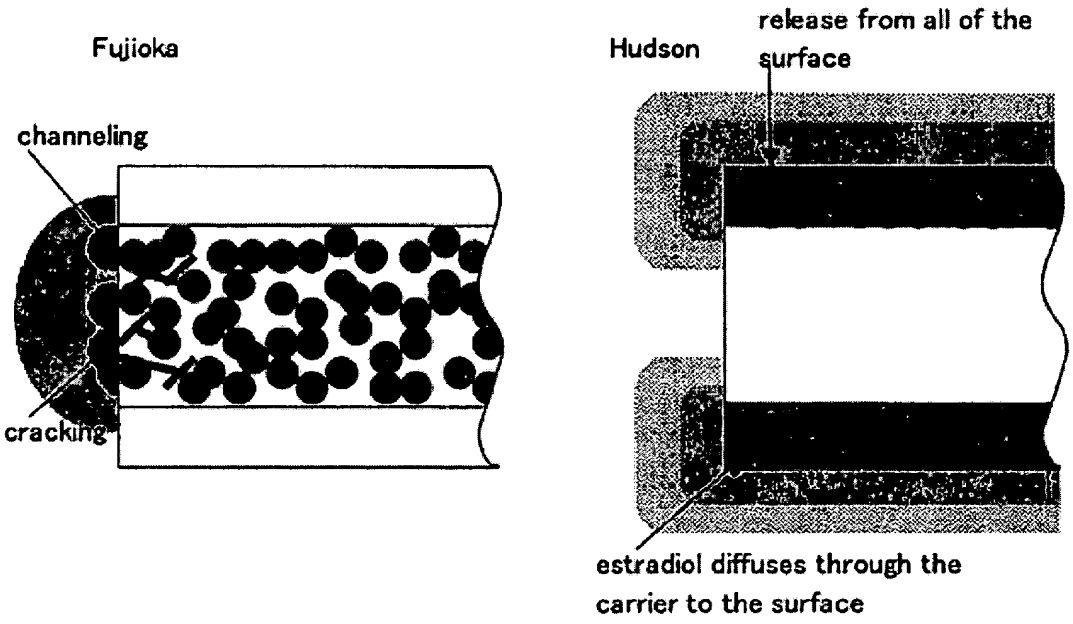
(II). Previously Presented Comments

The structure of the formulation disclosed in Fujioka et al. and Hudson et al. are as schematically shown below, respectively. Hudson et al. teaches a cylindrical implantable formulation comprising estradiol as a drug. However, estradiol is not a water-soluble drug but a lipophilic drug. Accordingly, the combination of Fujioka et al. and Hudson et al. might motivate one skilled in the art to prepare an implantable preparation wherein a lipophilic drug is comprised in the outermost layer. However, the preparation as instantly claimed wherein the outermost layer comprises a water-soluble drug was not obvious at the time the invention was made.



A crosssectional view before implantation

Furthermore, Fujioka et al. teaches that a channeling phenomenon participates in the release process for water-soluble drugs from hydrophobic polymer carriers. Here, the drug present in the vicinity of the surface of the formulation first dissolves in the ambient water (see col. 1, lines 47-56 of Fujioka et al.; and also see page 59, right column, lines 13-31 of *Journal of Controlled Release* 66 (2000), 49-61). Thus, long-term zero-order release of the water-soluble drug from the formulation of Fujioka is achieved by such process as schematically shown below. On the other hand, in the preparation of Hudson, estradiol diffuses through dimethylpolysiloxane silicone rubber to the surface where it is released into the animal tissue, as schematically shown below (see page 4, lines 1-4 of Hudson et al.).



A crosssectional view after implantation

Thus, when estradiol is used in the formulation of Fujioka et al., one of ordinary skill in the art would anticipate that estradiol diffuses through dimethylpolysiloxane rubber, such as Dow Corning® MDX 4-4210, to the surface, whichever it is comprised in an inner layer or the outermost layer. Such diffusion of estradiol through dimethylpolysiloxane rubber would not provide zero-order release since estradiol released from the formulation was decreased over time, as shown in the table disclosed in Hudson (page 8). Therefore, the teaching of Hudson would not motivate one of ordinary skill in the art to apply estradiol to the formulation of Fujioka, in order to provide a multiple drug delivery system that achieves a zero-order release profile over an extended period of time.

CONCLUSION

Accordingly, based upon the above considerations, the Examiner is respectfully requested to reconsider the outstanding rejection under 35 USC § 103 and to issue a Notice of Allowance clearly indicating the patentability of each of pending claims 1-8.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact John W. Bailey (Reg. No. 32,881) at the telephone number below.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

JUL 6 2005

Respectfully submitted,

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JWB/enm
0020-4771P

Enclosures: E.F. Reynolds, MARTINDALE, The Extra Pharmacopoeia, 29th Ed., page 1407(1989); and
T.H. Ferguson et al., Journal of Controlled Release, 8, pages 45-54 (1988).

MARTINDALE

The Extra Pharmacopoeia

Twenty-ninth Edition

Edited by James E. F. Reynolds

Deputy Editor
Kathleen Parfitt

Assistant Editors
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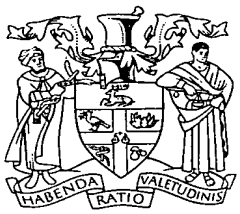

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1989

and other menstrual disorders, it is given in a dosage of 5 to 10 mg daily usually from the 5th to the 24th day of the cycle; 20 to 30 mg may be required for the initial control of bleeding. In the treatment of endometriosis the usual initial dose is 5 to 10 mg daily increased to 20 mg daily and maintained for at least 6 to 9 months. Doses of up to 40 mg may be given to control breakthrough bleeding.

Proprietary Names and Manufacturers

The following names have been used for multi-ingredient preparations containing norethynodrel—Conovid *(Searle, UK)*; Conovid-E *(Searle, Austral.; Searle, S.Afr.; Searle, UK)*; Elan *(Valeas, Ital.)*; Enavid *(Searle, Neth.; Searle, UK)*; Enavid-E *(Searle, Arg.; Searle, Neth.; Searle, UK)*; Enovid 5 mg *(Searle, USA)*; Enovid-E *(Searle, Canad.; Searle, USA)*; Kontrazeptivum 63-ratiopharm *(Ratiopharm, Ger.)*; Novinol *(Desbergers, Canad.)*; Ovarion *(Fher, Spain)*; Ovulen Novum *(Vita, Spain)*.

13031-z

Norgestimate *(BAN, USAN, rINN).*

D-138; Dexnorgestrel Acetime; ORF-10131. 13β-Ethyl-3-hydroxyimino-18,19-dinor-17α-pregn-4-en-20-yn-17β-yl acetate.

$C_{23}H_{31}NO_3 = 369.5$.

CAS — 35189-28-7.

Norgestimate is a progestogen with actions and uses similar to those described for the progestogens in general (see p.1386).

Proprietary Names and Manufacturers

Ortho Pharmaceutical, USA.

The following names have been used for multi-ingredient preparations containing norgestimate— Cilest *(Cilag, Ger.)*.

9080-w

Norgestrel *(BAN, USAN, rINN).*

dl-Norgestrel; DL-Norgestrel; Wy-3707. (±)-13-Ethyl-17β-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one.

$C_{21}H_{28}O_2 = 312.5$.

CAS — 6533-00-2.

Pharmacopoeias. In *Chin., Nord.*, and *U.S.*

A white or practically white, practically odourless crystalline powder. Practically **insoluble** in water; sparingly soluble in alcohol; freely soluble in chloroform.

9081-e

Levonorgestrel *(BAN, USAN, rINN).*

D-Norgestrel; Wy-5104. The (−)-isomer of norgestrel.

CAS — 797-63-7.

NOTE. The name Dexnorgestrel has been used.

Pharmacopoeias. In *Br., Nord.*, and *U.S.*

A white or almost white, odourless or almost odourless, crystalline powder. Practically **insoluble** in water; slightly soluble in alcohol, acetone, and ether; soluble 1 in 45 of chloroform. **Store** at a temperature not exceeding 15°. Protect from light.

Adverse Effects and Precautions

As for the progestogens in general, p.1386.

See also under hormonal contraceptives, p.1387.

EFFECTS ON THE SKIN. A sudden onset of moderate to severe papulopustular acne was noted in about 20 patients taking norgestrel in an oral contraceptive preparation, and was considered to be due to norgestrel being an androgen-dominant progestogen.— R. K. Woodward, *Archs Derm.*, 1974, *110*, 812.

PREGNANCY AND THE NEONATE. *Effects on the foetus.* A 23-year-old woman who had taken norgestrel and ethinyloestradiol for the first 3 months of pregnancy gave birth to an infant with a tracheo-oesophageal fistula.— O. Frost, *Br. med. J.*, 1976, *2*, 978.

Inoperable hepatoblastoma in a 7-month-old male infant might have been associated with ingestion of norgestrel 30 μg daily by the mother during the first 3 months of pregnancy.— J. Otten *et al.* (letter), *New Engl. J. Med.*, 1977, *297*, 222.

Absorption and Fate

Norgestrel and levonorgestrel are absorbed from the gastro-intestinal tract. Metabolites are excreted in the urine and faeces as glucuronide and sulphate conjugates.

PREGNANCY AND THE NEONATE. The concentration of D-norgestrel in milk was about 15% of that in plasma; it could not be detected in the milk of women taking only 30 μg daily.— S. Nilsson *et al.*, *Am. J. Obstet. Gynec.*, 1977, *129*, 178.

Uses and Administration

Norgestrel and levonorgestrel are progestogens with actions and uses similar to those described for the progestogens in general (see p.1386). They are more potent as inhibitors of ovulation than norethisterone and have androgenic activity. Levonorgestrel is the active isomer; norgestrel, the racemate, has therefore half the potency of levonorgestrel.

They are both used as the progestogenic component of combined oral contraceptives and are also used as progestogen-only types of oral contraceptives (see p.1391).

Either norgestrel or levonorgestrel are also used as the added progestogen to oestrogenic therapy in menopausal disorders.

Preparations

Levonorgestrel and Ethinyl Estradiol Tablets *(U.S.P.).* Tablets containing levonorgestrel and ethinyloestradiol.

Norgestrel Tablets *(U.S.P.)*

Norgestrel and Ethinyl Estradiol Tablets *(U.S.P.).* Tablets containing norgestrel and ethinyloestradiol.

Proprietary Preparations

Proprietary preparations containing norgestrel or levonorgestrel are described under conjugated oestrogens (p.1409) and under oestradiol valerate (p.1408).

Proprietary contraceptive preparations containing norgestrel or levonorgestrel are described under the section on hormonal contraceptives (p.1392)

Proprietary Names and Manufacturers of Norgestrel and Levonorgestrel

Follistrel *(Kabi, Swed.)*; Microlut *(Schering, Austral.; Schering, Belg.; Schering, Ger.; Schering, Ital.; Switz.)*; Microluton *(Schering, Denm.; Leiras, Fin.; Schering AG, Norw.; Swed.)*; Microval *(Wyeth, Austral.; Wyeth, Belg.; Wyeth, Denm.; Wyeth, Fin.; Wyeth-Byla, Fr.; Wyeth, S.Afr.; Wyeth, UK)*; Mikro-30 *(Wyeth, Ger.)*; Neogest *(Schering, UK)*; Norgeston *(Schering, UK)*; Norplant *(Leiras, Fin.; Leiras, Swed.)*; Ovrette *(Wyeth, USA)*.

The following names have been used for multi-ingredient preparations containing norgestrel and levonorgestrel— Adepal *(Wyeth-Byla, Fr.)*; Binordiol *(Wyeth, Belg.; Wyeth, Denm.; Wyeth, Fin.; Wyeth, Ital.; Wyeth, Neth.; Wyeth, Switz.)*; Biphasil *(Wyeth, Austral.; Wyeth, S.Afr.)*; Bivlar *(Schering, Ital.)*; Cyclo-Progynova *(Schering, UK)*; Duoluton *(Schering, Arg.; Schering, Austral.)*; Ediwal *(Schering, Ger.)*; Egogyn 30 *(Schering, Ital.)*; Eugynon *(Schering, Arg.; Schering, Austral.; Belg.; Schering, Denm.; Schering, Ger.; Schering, Ital.; Neth.; Schering, Norw.; Schering, S.Afr.; Schering, Spain; Schering, Switz.)*; Eugynon 30 *(Schering, UK)*; Eugynon 50 *(Schering, UK)*; Evanor-d *(Wyeth, Ital.)*; Evelea *(Elea, Arg.)*; Fironetta *(Schering, Denm.)*; Follimin *(KabiVitrum, Norw.; Kabi, Swed.)*; Follinett *(Kabi, Swed.)*; Gentrol *(Wyeth, Denm.)*; Gynatrol *(Wyeth, Denm.)*; Levlen *(Berlex, USA)*; Logynon *(Schering, UK)*; Logynon ED *(Schering, S.Afr.; Schering, UK)*; Lo/Ovral *(Wyeth, USA)*; Microgyn *(Schering, Denm.)*; Microgynon *(Schering, Arg.; Schering, Austral.; Leiras, Fin.; Schering, Ger.; Schering, Ital.; Schering, Norw.; Schering, Spain)*; Microgynon 30 *(Schering, Belg.; Schering, Neth.; Schering, Switz.; Schering, UK)*; Microgynon 50 *(Schering, Belg.; Schering, Neth.; Schering, Switz.)*; Microgynon ED *(Schering, Austral.)*; Minidril *(Wyeth-Byla, Fr.)*; Min-Ovral *(Wyeth, Canad.)*; Neogentrol *(Wyeth, Denm.)*; Neo-Gentrol *(Wyeth, Fin.)*; Neogynon *(Schering, Arg.; Schering, Austral.; Schering, Belg.; Schering, Denm.; Schering, Ger.; Schering, Neth.; Schering, Switz.)*; Neogynona *(Schering, Spain)*; Neo-Primovlar *(Leiras, Fin.)*; Neo-Stediril *(Wyeth, Belg.; Wyeth, Ger.; Wyeth, Neth.; Wyeth, Switz.)*; Neovlar *(Swed.)*; Neovletta *(Schering, Swed.)*; Nordette *(Wyeth, Arg.; Wyeth, Austral.; Wyeth, S.Afr.; Wyeth, USA)*; Nordiol *(Wyeth, Arg.; Wyeth, Austral.; Wyeth, S.Afr.)*; Normovlar *(Schering, S.Afr.)*; Novogyn *(Schering, Ital.)*; Ovoplex *(Orfi, Spain)*; Ovral *(Wyeth, Arg.; Wyeth, Austral.; Wyeth, Canad.; Wyeth, S.Afr.; Wyeth, USA)*; Ovran *(Wyeth, UK)*; Ovran 30 *(Wyeth, UK)*; Ovranet *(Wyeth, Ital.)*; Ovranette *(Wyeth, UK)*; Perikursal *(Wyeth, Ger.)*; Prempak *(Ayerst, UK)*; Prempak-C *(Ayerst, UK)*; Primovlar *(Swed.)*; Prolorfin *(Orfi, Spain)*; Regunon *(Schering, Swed.)*; Schering PC4 *(Schering, UK)*; Sekvilar *(Leiras, Fin.)*; Sequilar *(Schering, Austral.; Schering, Belg.; Schering, Ger.; Schering, Neth.; Schering, Switz.)*; Sequilarum *(Schering, Denm.; Schering, Swed.)*; Stediril *(Wyeth, Belg.; Wyeth-Byla, Fr.; Wyeth, Ger.; Wyeth, Switz.)*; Stediril 30 *(Wyeth, Belg.; Wyeth, Ger.; Wyeth, Neth.; Wyeth, Switz.)*; Stediril-d *(Wyeth, Belg.; Wyeth, Ger.; Wyeth, Neth.; Wyeth, Switz.)*; Tetragynon *(Schering, Switz.)*; Triagynon *(Schering, Spain)*; Triciclor *(Orfi, Spain)*; Tridestan *(Gador, Arg.)*; Trigynon *(Schering, Belg.; Schering, Ital.; Schering, Neth.)*; Trikvilar *(Leiras, Fin.)*; Tri-Levlen *(Berlex, USA)*; Trinordiol *(Wyeth, Arg.; Wyeth, Belg.; Wyeth, Denm.; Wyeth, Fin.; Wyeth-Byla, Fr.; Wyeth, Ger.; Wyeth, Ital.; Wyeth, Neth.; KabiVitrum, Norw.; Kabi, Swed.; Wyeth, Switz.; Wyeth, UK)*; Trionetta *(Schering, Norw.; Schering, Swed.)*; Triphasil *(Wyeth, Austral.; Wyeth, Canad.; Wyeth, S.Afr.; Wyeth, USA)*; Triquilar *(Schering, Arg.; Schering, Austral.; Schering, Denm.; Schering, Ger.; Schering, Switz.)*; Tristep *(Asche, Ger.)*.

13032-c

Norgestrienone *(rINN).*

17β-Hydroxy-19-nor-17α-pregna-4,9,11-trien-20-yn-3-one.

$C_{20}H_{22}O_2 = 294.4$.

CAS — 848-21-5.

Adverse Effects and Precautions

As for the progestogens in general, p.1386.

Uses and Administration

Norgestrienone is a progestogen with actions and uses similar to those of the progestogens in general (see p.1386). It is used as the progestogenic component of some combined oral contraceptives and is also used as a progestogen-only type of oral contraceptive (see p.1391).

Proprietary Names and Manufacturers

Ogyline *(Roussel, Fr.)*.

The following names have been used for multi-ingredient preparations containing norgestrienone— Planor *(Roussel, Fr.)*.

9082-l

Normethandrone

Methylestrenolone; Methylnortestosterone; Normethandrolone. 17β-Hydroxy-17α-methylestr-4-en-3-one.

$C_{19}H_{28}O_2 = 288.4$.

CAS — 514-61-4.

Normethandrone has progestogenic properties (see p.1386) and has been given by mouth in doses of 5 mg daily.

Proprietary Names and Manufacturers

Orga-Steron *(Organon, Belg.; Organon, Neth.)*.

9083-y

Oestradiol *(BAN).*

Beta-oestradiol; Dihydrofolliculine; Dihydrotheelin; Dihydroxyoestrin; Estradiol *(USAN, rINN).* ←

Estra-1,3,5(10)-triene-3,17β-diol.

$C_{18}H_{24}O_2 = 272.4$.

CAS — 50-28-2.

Pharmacopoeias. In *Aust., Fr., Mex., Span., Turk.*, and *U.S.*

White or creamy-white, odourless, hygroscopic crystals or crystalline powder. Practically **insoluble** in water; soluble 1 in 28 of alcohol, 1 in 435 of chloroform, and 1 in 150 of ether; soluble in acetone, dioxan, and solutions of fixed alkali hydroxides; sparingly soluble in vegetable oils. **Store** in airtight containers. Protect from light. ←

9084-j

Oestradiol Benzoate *(BANM).*

Beta-estradiol Benzoate; Dihydroxyoestrin Monobenzoate; Estradiol Benzoate *(rINN)*; Estradioli Benzoas. Estra-1,3,5(10)-triene-3,17β-diol 3-benzoate.

$C_{25}H_{28}O_3 = 376.5$.

CAS — 50-50-0.

Pharmacopoeias. In *Arg., Aust., Belg., Br., Braz., Chin., Cz., Egypt., Eur., Fr., Ger., Hung., Ind., Int., It., Jpn, Jug., Mex., Neth., Nord., Pol., Port., Roum., Span., Swiss*, and *Turk.* Also in *B.P. Vet.*

Colourless crystals or a white or almost white

Journal of Controlled Release, 8 (1988) 45–54
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COMPUDOSE®: AN IMPLANT SYSTEM FOR GROWTH PROMOTION AND FEED EFFICIENCY IN CATTLE*

T.H. Ferguson, G.F. Needham and J.F. Wagner**
Lilly Research Laboratories, P.O. Box 708, Greenfield, IN 46140 (U.S.A.)

COMPUDOSE® *is a polymeric controlled release device designed for the continuous delivery of estradiol-17β, a naturally occurring estrogenic hormone. The estrogen provided by* COMPUDOSE® *when implanted subcutaneously in the ear improves growth rate and feed efficiency in beef cattle. In vitro estradiol release studies were done to verify matrix diffusion-controlled estradiol release. The in vitro data compared favorably to in vivo estradiol release determined either by implant weight loss or from drug depletion zone measurements. An in vitro–in vivo correlation of 1.17 was determined. These studies demonstrated that the estradiol release from both the* COMPUDOSE® *200 and* COMPUDOSE® *400 products was identical for 270 days in vitro and 308 days in vivo.*

INTRODUCTION

COMPUDOSE® is a polymeric controlled release implant for the controlled delivery of estradiol to improve both growth rate and feed efficiency in beef cattle [1,2]. Since the early 1950s, compressed tablet implants containing estrogenic anabolics have been used to improve rate of gain and feed conversion in beef cattle for 2–3-month periods. However, because of the controlled release properties inherent in COMPUDOSE®, efficacy from the use of this controlled release implant is improved beyond approximately 84 to 100 days post-implantation when compared to compressed tablet implants [1]. Reimplantation of compressed tablets at approximately seventy days yields similar rate of gains and feed efficiencies to a single COMPUDOSE® implantation [1]. Thus, by using COMPUDOSE® implants one does not require a reimplantation program to achieve maximum anabolic response over 50 to 200 days.

In this paper we review the COMPUDOSE® implant properties and present the *in vitro and in vivo* estradiol release data generated to establish the mechanism of controlled estradiol release. An *in vitro–in vivo* correlation using these data will also be determined.

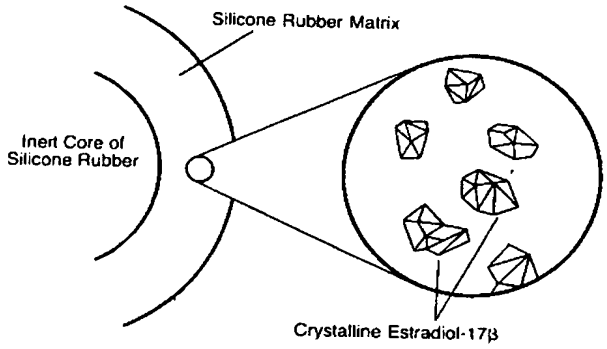
*Paper presented at the 14th International Symposium on Controlled Release of Bioactive Materials, August 2–5, 1987, Toronto, Ontario, Canada.

**To whom correspondence should be addressed.

MATERIALS AND METHODS

Theory

The general mathematical model (matrix-boundary diffusion layer) describing the release of drug which is homogeneously dispersed as discrete crystals or solid particles in a matrix has been presented previously [3–7]. This model is based upon Fick's first law of diffusion and the assumptions in the derivations include: (a) diffusion, not dissolution, is the primary



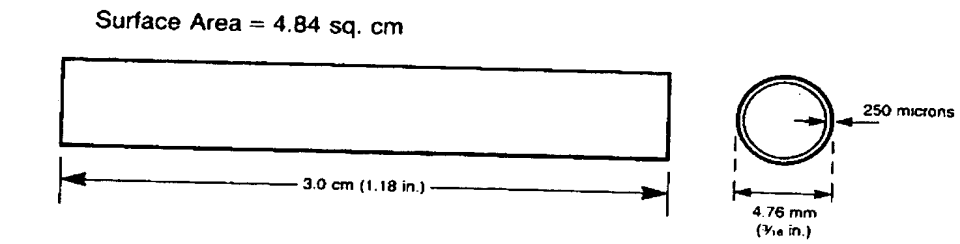


Fig. 1. COMPUDOSE® 200 product design. COMPUDOSE® 400 has a smaller inert silicone rubber core rod diameter and a nominal coating thickness of 500 μm (see Table 1).

TABLE 1

Estradiol controlled release implant nominal dimensions and values

	COMPUDOSE® 200	COMPUDOSE® 400
Implant diameter	4.76 mm	4.76 mm
Implant length	3.0 cm	3.0 cm
Implant weight	625 mg	620 mg
Drug content	24 mg	45 mg
Core rod diameter	4.19 mm	3.76 mm
Core rod density	1.18 g/cm^3	1.18 g/cm^3
Coating drug content	200 mg/g	200 mg/g
Coating density	1.13 g/cm^3	1.13 g/cm^3

mode of drug release, (b) the drug diffusion coefficient is constant irrespective of both the distance traveled within the matrix and the difference in concentration, (c) the diffusional process occurs through the matrix phase, not through pores or channels within the matrix, (d) the drug loading, A, is much greater than the drug's solubility in the matrix, C_s, and (e) a pseudo-steady state exists.

For a cylindrical device, the cumulative amount of drug, Q, released from the drug depletion zone is defined by [3]

$$Q = \pi h A (a_0^2 - a_1^2) \tag{1}$$

where: Q = amount of drug released (mg), h = height of cylinder (cm), A = concentration of drug in matrix (mg/cm^3), a_0 = outside radius of cylinder (cm), and a_1 = distance from center of cylinder to receding crystalline drug depletion boundary (cm).

The time-dependent change in the drug depletion zone can be expressed as [3]

$$\frac{a_1^2}{2} \ln \frac{a_1}{a_0} + \tfrac{1}{4}(a_0^2 - a_1^2) + \frac{D_e h_a}{2KD_a a_0}(a_0^2 - a_1^2) = \frac{C_s D_e t}{A} \tag{2}$$

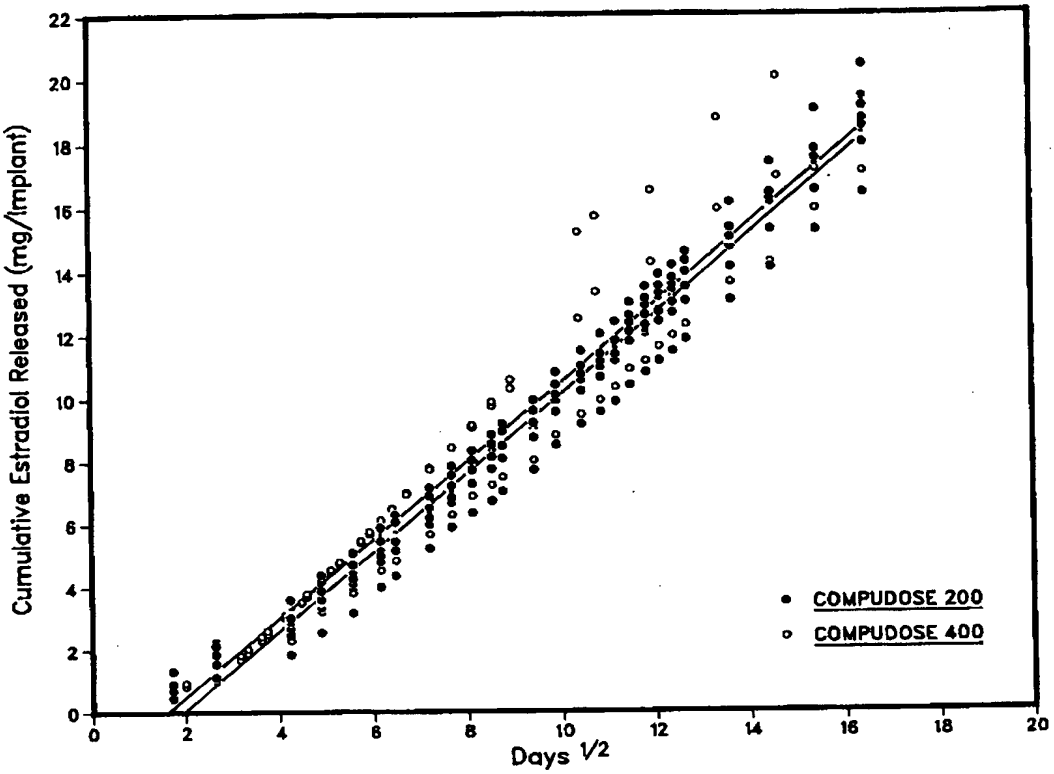


Fig. 2. *In vitro* estradiol release from COMPUDOSE® implants.

where: D_e = effective diffusion coefficient in the matrix (cm^2/s), h_a = hydrodynamic boundary layer (cm), K = partition coefficient (C_a/C_s), C_a = aqueous solubility (mg/cm^3), C_s = matrix solubility (mg/cm^3), D_a = diffusion coefficient in aqueous phase (cm^2/s), and t = time (s).

For a matrix diffusion-controlled process, i.e., if the partition coefficient K is large and/or if the hydrodynamic boundary layer h_a is small, or if the thickness of the drug depletion zone ($a_0 - a_1$) after a finite time becomes sufficiently large, then eqn. (2) reduces to [3]

$$\frac{a_1^2}{2} \ln \frac{a_1}{a_0} + \tfrac{1}{4} (a_0^2 - a_1^2) = \frac{C_s D_e t}{A} \qquad (3)$$

However, it has been suggested that one-dimensional diffusion from a plane surface is a good approximation for up to 50% of the drug released from a cylinder [4]. Since the estradiol in COMPUDOSE® is located in a peripheral coating of the implant cylinder representing not more than 38% of the total volume of the cylinder, then the release of estradiol from COMPUDOSE® implants can be adequately modeled using the expressions predicting drug release from a plane [4]

$$Q' = (2AD_eC_st)^{1/2} \qquad (4)$$

where: Q' = amount of drug released/unit surface area (mg/cm^2).

The drug depletion zone time dependency can then be expressed as

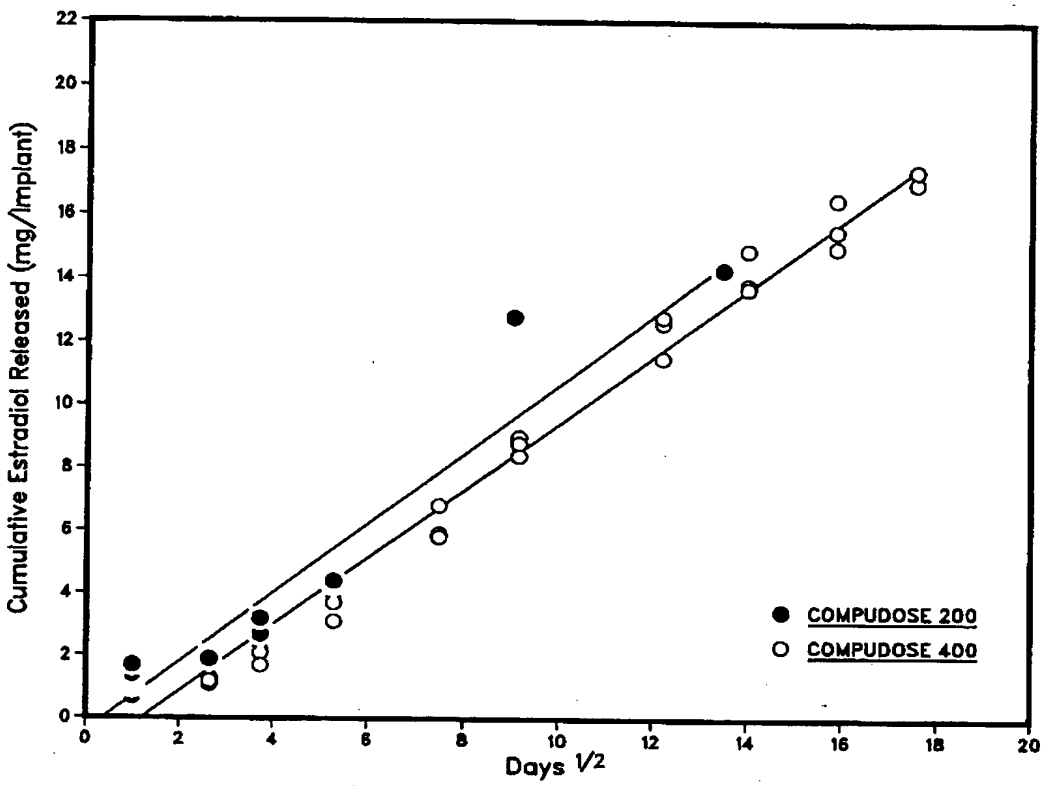


Fig. 3. *In vivo* estradiol release from COMPUDOSE® implants.

$$a_0 - a_1 = l \approx \left(\frac{2C_s D_e t}{A}\right)^{1/2} \quad (5)$$

Equations (4) and (5) indicate that, after a finite time, the matrix diffusion-controlled process becomes the predominant mechanism of drug release. The cumulative amount of drug release, Q', from a unit surface area becomes directly proportional to the square root of time ($t^{1/2}$).

EXPERIMENTAL

The COMPUDOSE® implant is made in a continuous process by coating a nonmedicated silicone rubber core with a thin layer of silicone rubber (MDX-4-4210 Clean Grade Elastomer, Dow Corning) which contains micronized crystalline estradiol-17β, USP. A laser photo-optic system monitors the diameter of the coated product prior to curing in a heated tower. The cured continuous strand of coated silicone rubber is then cut into 3-cm lengths by an automated cutter that rejects those implants that are outside preset product diameter limits. The dimensions of the controlled release implant are monitored so that the curved surface area for estradiol release is between the limits of 4.30 and 4.80 cm^2. Dependent upon the medicated coating thickness, the controlled release implant will release estradiol for a minimum of either 200 days (COMPUDOSE® 200) or 400 days (COMPUDOSE® 400). A schematic drawing and nominal implant dimensions and specifications are shown in Fig. 1 and Table 1, respectively.

Prior to packaging, production implants are coated with a small quantity of oxytetracycline

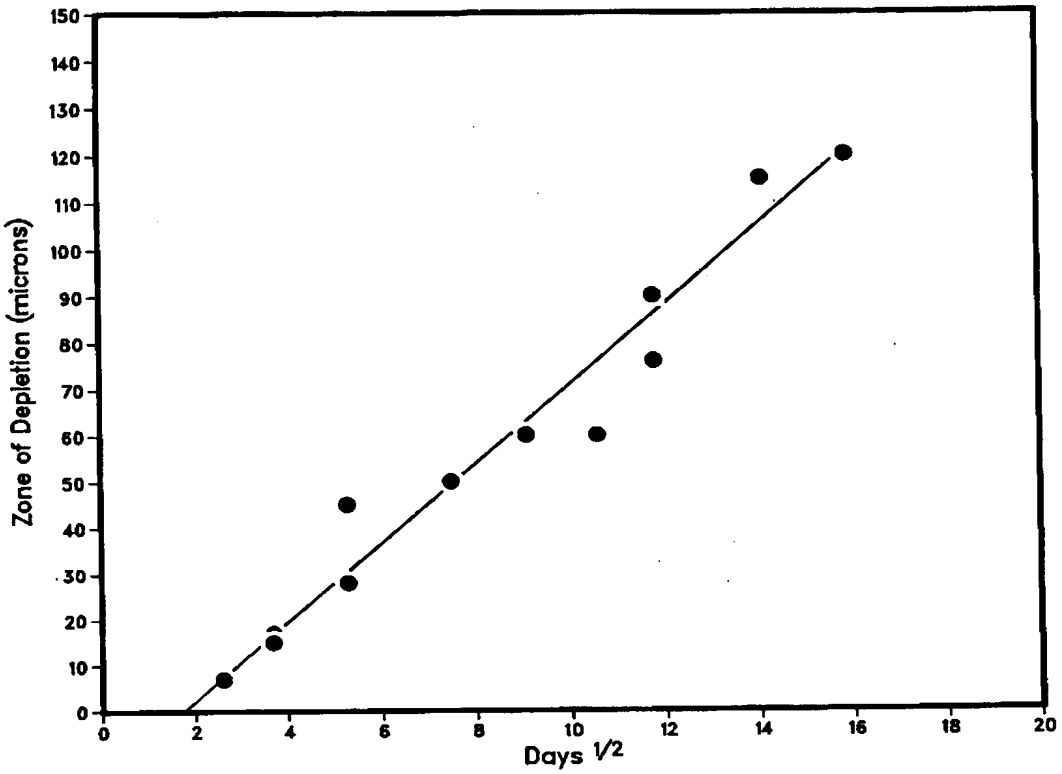


Fig. 4. Estradiol depletion zone in COMPUDOSE® implants retrieved from the ears of steers.

HCl, USP, to decrease infection at the site of implantation and aid implant retention [8]. Because of the high aqueous solubility of the oxytetracycline HCl, the antibacterial dissolves rapidly and does not impede estradiol release from the implant.

Both the 200- and 400-day products were evaluated in the *in vitro* and *in vivo* studies. For the *in vitro* studies, twenty-four implants selected from eight COMPUDOSE® 200 production lots and twelve implants selected from four COMPUDOSE® 400 production lots were evaluated for estradiol release. Each implant was placed into closed glass containers with 100 ml of an aqueous solution of 0.5% sodium dodecyl sulfate (SDS) and stored at 39°C in a shaker bath operating at approximately 120 rpm. The solubility of estradiol in the SDS solution was determined to be approximately 136 μg/ml. The SDS solution was chosen because sink conditions could be maintained. The total SDS elution medium was changed periodically to maintain sink conditions and assayed for estradiol content spectrophotometrically (280 nm). The cumulative mass of estradiol released at each assay period was calculated for each implant. These studies continued for approximately 270 days.

For the *in vivo* studies, numerous implants selected from approximately sixteen COMPUDOSE® 200 and COMPUDOSE® 400 production lots were implanted subcutaneously into the ears of cattle for up to 308 days. Placebo (nonmedicated) silicone rubber implants of the same dimensions were also implanted subcutaneously in the ears of steers. Prior to implantation, individual implants were identified and weighed. Individual implants were removed

TABLE 2

Summary of depletion zone measurements and calculated mass of estradiol release using eqn. (1)

Days implanted	Zone of depletion (μm)[a]	Calculated estradiol released (mg)[b]
10	7	0.71
14	15, 17[c]	1.53, 1.73[c]
28	28, 45	2.85, 4.58
56	50	5.09
82	60	6.10
112	60	6.10
139	76	7.73
140	90	9.15
200	115	11.70
203	114	11.59
253	120	12.20

[a]Values given represent means of eight separate measurements taken per implant per time period.
[b]Values were calculated using eqn. (1) assuming $A = 226$ mg/cm^3, $h = 3$ cm and $a_0 = 2.38$ mm.
[c]More than one depletion zone measurement was made on implants from more than one lot of COMPUDOSE® at 14 and 28 days. The variation in the numbers reported point to the inherent difficulty in accurately determining depletion zones at the microscopic level.

from the ears after predetermined times had elapsed, rinsed in distilled water, dried to a constant weight in a vacuum oven and then weighed. The estradiol released *in vivo* was determined by the difference between the initial and final implant weights corrected for placebo implant weight differences. Previous studies had documented that implant weight loss was predictive of estradiol release [9].

The *in vitro* and *in vivo* data were tested for conformance to eqn. (4) by means of SAS PROC GLM (SAS Release 82.2 Statistical Analysis System, SAS Institute, Cary, North Carolina).

Selected implants from the *in vivo* studies were further characterized for their drug depletion zone. As estradiol diffuses from the matrix, reasonably well-defined depletion zones of crystalline estradiol develop. At longer release times larger zones develop. Vacuum-dried implants were cross-sectioned and sputter-coated with gold–palladium. The zones of depletion were measured directly by scanning electron microscopy (Philips 501-B Scanning Electron Microscope, Mahwah, NJ). These data were tested for conformance to eqn. (5). In addition, an estimate of the cumulative mass of estradiol release was obtained using eqn. (1). This can be done assuming the drug loading, A, is much greater than the drug solubility in the silicone rubber matrix, C_s.

RESULTS

Figure 2 shows the cumulative *in vitro* estradiol release as a function of the square root of time from COMPUDOSE® 200 and 400 implants into the 0.5% SDS elution medium at 39°C. Each data point represents the mean of three implants per lot. Linear regression lines are shown for both the 200- and 400-day products.

Figure 3 shows the cumulative *in vivo* estradiol release as a function of the square root of time for both COMPUDOSE® 200 and 400 implants. Each data point represents the mean of between 2 and 60 implants. Linear regression lines are shown for both the 200- and 400-day products.

Data from the drug depletion zone measurement are shown in Fig. 4. A linear regression line has been fitted to the depletion zone versus $t^{1/2}$ data in Fig. 4. Utilizing eqn. (1), the cumulative estradiol mass released was calculated based upon the depletion zone measurements. A summary of the drug depletion zone studies is shown in Table 2. An example of drug depletion zones at various times is illustrated in Fig. 5.

DISCUSSION

The *in vitro* data in Fig. 2 and statistical analysis support the matrix diffusion-controlled process for estradiol release from COMPUDOSE® implants, thus conforming to the

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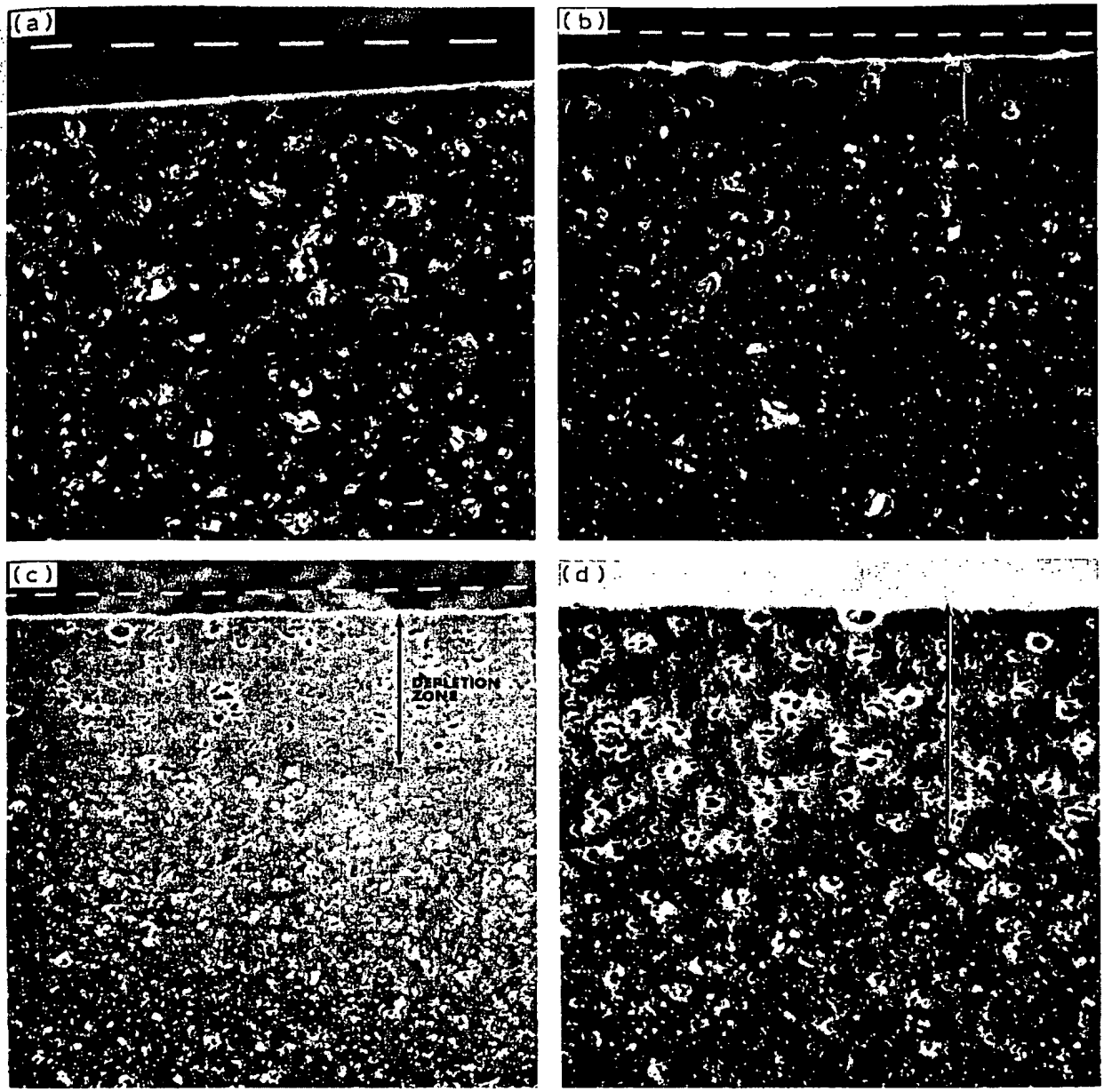

Fig. 5. Scanning electron photomicrographs of cross-sections of COMPUDOSE® implants showing drug depletion zones after implantation in the ears of steers: (a) 1 day, magnification = 700×, scale bar = 10 μm; (b) 28 days, magnification = 350×, scale bar = 10 μm; (c) 139 days, magnification = 350×, scale bar = 10 μm; (d) 253 days, magnification = 350×, scale bar = 10 μm.

predictive model described by eqn. (4). However, the slope and intercept parameters of the linear regression lines were statistically different for the 200- and 400-day products. The regression lines for the two products were:

COMPUDOSE® 200 $Q = 1.241t^{1/2} - 2.388$

COMPUDOSE® 400 $Q = 1.537t^{1/2} - 3.112$

Equation (4) predicts that COMPUDOSE® 400 implants would have a higher estradiol release rate compared to COMPUDOSE® 200 implants. This is due to the approximately 1.2% greater implant surface area for estradiol release on the cut ends of the COMPUDOSE® 400 implants. However, measured differences in estradiol release from the two implant types can rarely be expected to be recognized in view of the implant production specification limits and experimental variables. Back-diffusion of estradiol into the nonmedicated silicone rubber core would result in an equilibrium concentration of approximately 0.004 mg/cm^3 [10] or a total of 0.0006 mg and 0.0004 mg for COMPUDOSE® 200 and COMPUDOSE® 400 implants, respectively. The contribution to the total estradiol release rate due to back-diffusion of estradiol is insignificant and could not account for any observed differences in estradiol release rates between COMPUDOSE® 200 and 400 implants. Thus, for unknown reasons one of the four COMPUDOSE® 400 lots showed higher estradiol release at long time periods, contributing to the increased slope of the *in vitro* regression line for the 400 day product. Although the differences in the two regression lines for the two products were statistically significant, there is a question as to whether these differences were real. Accordingly, a single linear regression line describing both the 200- and 400-day products *in vitro* was generated:

$Q = 1.236t^{1/2} - 2.154$

Note that in Fig. 2 the Q versus early $t^{1/2}$ data are nonlinear. If the estradiol release was solely a matrix diffusion-controlled process, then the Q versus early $t^{1/2}$ data in Fig. 2 would be linear. However, this is not the case and the generalized model for matrix-boundary diffusion layer controlled release exists in which the drug depletion zone is so small (partition-controlled release) that a Q versus t relationship is observed [4]. Equations (1) and (2) predict the presence of this nonlinear Q versus $t^{1/2}$ region, the extent of which is governed by the magnitude of various physicochemical constants [4]. At later times (after approximately 6 days) the predominate process for estradiol release is matrix diffusion controlled.

The *in vivo* data in Fig. 3 and statistical analysis again support the matrix diffusion-controlled process for estradiol release from COMPUDOSE® implants, thus conforming to the theoretical model described by eqn. (4). The regression lines for the two products were:

COMPUDOSE® 200 $Q = 1.04t^{1/2} - 0.26$

COMPUDOSE® 400 $Q = 1.07t^{1/2} - 1.35$

Statistical analysis of the slope parameters of the linear regression lines for both the 200- and 400-day products showed no statistical difference. The analysis indicated that the use of a common slope for both COMPUDOSE® 200 and COMPUDOSE® 400 was justified, therefore:

$Q = 1.06t^{1/2} - 1.26$

The linear relationship between the crystalline estradiol depletion zone and $t^{1/2}$ as predicted by eqn. (5) was well established in Fig. 4. The equation for the regression line was $l = 8.6\ t^{1/2} - 14.8$. When the estradiol released was calculated using eqn. (1) in Table 2, we noted that the values were less than those experimentally derived *in vivo*. Because of the inherent problems accurately determining zones of depletion at the microscopic level this phenomenon is to be expected. As shown in Fig. 5, the zones of depletion are not always well defined and the extent of the depletion zone can be easily underestimated. Nonetheless, a regression line was generated for the calculated estradiol release data in Table 2, and:

TABLE 3

Experimentally derived estradiol release rates ($\mu g/cm^2/day^{1/2}$)

In vitro	*In vivo*	
	Implant weight loss	Depletion zone
255	220	180

$$Q = 0.87t^{1/2} - 1.48$$

Table 3 shows the estradiol release rates generated in the *in vitro*, *in vivo* and depletion zone studies and normalized for a nominal surface area of 4.84 cm^2. The estradiol release rates obtained were in surprising agreement. Utilizing the *in vivo* implant weight loss data, an *in vitro–in vivo* correlation can be defined as $(Q'/t^{1/2})$ *in vitro*/$(Q'/t^{1/2})$ *in vivo* = 1.17. Therefore, one day in the *in vitro* test system represented approximately 1.4 days *in vivo*. The fact that the correlation factor is so close to unity is remarkable and indicates that the *in vitro* test system was a good model for the prediction of *in vivo* subcutaneous estradiol release in the ear.

CONCLUSIONS

The release of estradiol from COMPUDOSE® controlled release implants was found to be predominately matrix diffusion controlled both *in vitro* and when implanted subcutaneously in ears of cattle. A linear Q' versus $t^{1/2}$ relationship was observed. At early time periods of 6 days or less, however, the *in vitro* data supported the matrix-boundary diffusion layer model as described by eqns. (1), (2) and others [3,4,6]. Estradiol release rate comparisons from both COMPUDOSE® 200 and COMPUDOSE® 400 implants in the *in vitro* test system and *in vivo* were made. The estradiol release rate from both products was identical. This conclusion should have been expected as the coating estradiol concentrations for both products were the same, the total estradiol content changed by varying the thickness of the coating layer. Thus, estradiol release from both COMPUDOSE® 200 and 400 implants would be expected to be comparable until the COMPUDOSE® 200 implants were depleted. Measurement of the drug depletion zones by scanning electron microscopy of retrieved implants from the ears of cattle indicated that a linear drug depletion zone thickness versus $t^{1/2}$ relationship existed, as predicted by eqn. (5). Experimentally derived estradiol release rates from the *in vitro* and *in vivo* release studies and the calculated estradiol release rate from the drug depletion zone study agreed with each other. The *in vitro–in vivo* correlation was determined as 1.17, demonstrating that the *in vitro* test system was a good model for predicting *in vivo* subcutaneous release of estradiol in the ear.

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REFERENCES

1 R.P. Basson, W.E. Dinusson, L. Embry, D.L. Feller, P.E. Gorham, H.P. Grueter, D.D. Hinman, J. McAskill, C. Parrott, J. Riley, T.L. Stanton, D.C. Young and J.F. Wagner, Comparison of the performance of estradiol silicone rubber implant-treated steers to that of zearalanol or estradiol + progesterone, J. Anim. Sci., 61 (1985) 1023–1029.

2 J.F. Wagner, R.P. Basson, L.H. Carroll, J.L. Hudson, J. McAskill, R.S. Nevin and A.P. Raun, Factors effecting payout of estradiol 17β ($E_2\beta$) from silicone rubber implant and effect on performance in finishing steers, 71st Annual Meeting of the American Society of Animal Science, Tucson, AZ, 1979, p. 416.

3 T.J. Roseman and W.I. Higuchi, Release of medroxyprogesterone acetate from silicone polymer, J. Pharm. Sci., 59 (1970) 353–357.

4 T.J. Roseman, Release of steroids from a silicone polymer, J. Pharm. Sci., 61 (1972) 46–50.
5 Y.W. Chien, H.J. Lambert and T.K. Lin, Solution-solubility dependency of controlled release of drug from polymer matrix: Mathematical analysis, J. Pharm. Sci., 64 (1975) 1643–1647.
6 Y.W. Chien, Novel Drug Delivery Systems, Marcel Dekker, New York, NY, 1982.
7 T.J. Roseman, Pharmaceutical devices and method, U.S. Patent 3,920,805, November 18, 1975.
8 J.C. Parrott, R.P. Basson, L.H. Carroll, N.G. Elliston, T.H. Ferguson, P.E. Gorham, H.P. Grueter, J.W. McAskill and J.F. Wagner, Factors affecting retention of estradiol-17β silicone rubber implants in ears of steers, J. Anim. Sci., 61 (1985) 807–813.
9 R.C. Davis and T.H. Ferguson, *In vitro* release of estradiol and weight loss of individual COMPUDOSE® implants, unpublished data.
10 T.J. Roseman, Theoretical analysis of COMPUDOSE® 365, unpublished data.

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